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(54) Title: SYNTHESIS OF L–RIBOSE AND 2–DEOXY L–RIBOSE

(57) Abstract

A method for synthesizing L–ribose (1) and 2–deoxy L–ribose (12) from inexpensive D–ribose (2) is provided. The 5–*O*–trityl ribose (3) (prepared in 70 % yield from D–ribose) is reduced with borohydride to give the tetrol (4), which is then peracetylated to the tetraacetate (5). Hydrolysis of the trityl ether followed by Swern oxidation affords the aldehyde (7) via the alcohol (6). This aldehyde is a protected form of L–ribose, being L–ribose 2,3,4,5,–tetraacetate. Mild basic hydrolysis of the acetate affords L–ribose itself (1), thus ending an efficient six–step synthesis of (1) from (2) which proceeds in 39 % overall yield. In a second aspect of the invention, L–ribose is converted into the β–selenophenyl ribofuranoside (10) via the tetraester (9) in 71 % isolated yield for the four steps. Treatment of (10) with tributylstannane and AIBN furnishes in 84 % yield the tribenzoyl 2–deoxy–L–ribofuranoside (11) which, on basic hydrolysis, gives 2–deoxy L–ribose (12) in high yield. In a third aspect of the invention, L–arabinose (13) is converted into 2–deoxy L–ribose (12) via the arabinopyranosyl bromide (14), via similar reductive rearrangement with tributylstannane to give the 2–deoxy ribopyranose tribenzoate (16). Hydrolysis yields 2–deoxy L–ribose. In a third aspect of the invention, L–arabinose is converted into 2–deoxy L–ribose by an alternate route.

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SYNTHESIS OF L-RIBOSE AND 2-DEOXY L-RIBOSE

Acknowledgment of Government Support

This invention was made with government support under Grant No. GM 47228 awarded by the National Institutes of Health. The U.S. Government has certain rights in the invention.

Cross-reference to Related Application

This application is based on, and claims priority of, U.S. provisional application No. 60/040,270, filed March 15, 1997, the contents of which are incorporated herein by this reference.

Field of the Invention

This invention relates generally to carbohydrate synthesis and, more particularly, to the synthesis of L-ribose and a 2-deoxy derivative.

Background of the Invention

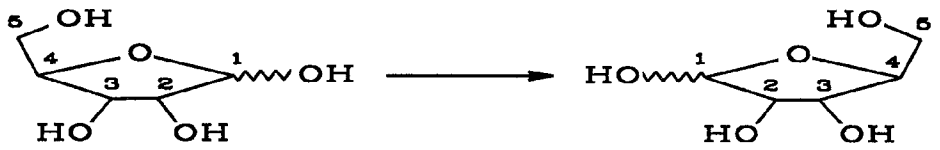
In the last few years, the use of L-carbohydrates and their derived nucleosides in medicinal applications has greatly increased. In particular, several modified nucleosides derived from L-sugars, e.g., L-5-fluoro-2', 3'-dideoxycytidine and L-2', 3'-dideoxycytidine (L-5FddC and L-ddC), have shown great potential as useful antiviral agents. They possess good antiviral activity but greatly reduced toxicity. In addition, several antisense oligonucleotide therapy approaches utilize L-nucleosides, either normal L-RNA or 2'-deoxy L-DNA as materials to bind pieces of D-RNA.

L-ribose is the enantiomer of D-ribose, which occurs naturally. Several syntheses of L-ribose are known. The most direct synthetic methodology currently available begins with L-arabinose and proceeds in about 30% yield after a difficult separation from unreacted L-arabinose and other carbohydrates. Because L-sugars offer tremendous potential in many medicinal applications, a need exists for an improved synthesis of L-ribose and its derivatives.

Summary of the Invention

The present invention provides a unique synthetic route for making L-ribose **(1)** and its derivatives, beginning with the natural enantiomer, D-ribose **(2)**. The two sugars differ only in their respective groups at C1 and C5, with C2, C3 and C4 being identical. The overall

route provided by the invention is the conversion of **(2)** into **(1)**, as shown in the following scheme, where the sugars are drawn in their cyclic, ribofuranose configurations:



(2) **(1)**

Thus, the present invention provides a method for converting inexpensive, naturally occurring D-ribose into L-ribose, by interconverting the hydroxy group at C1 and the hydroxymethyl group at C5. In an exemplary embodiment of the invention, this proceeds by oxidizing the hydroxymethyl group at C5 to an aldehyde, and reducing the pseudo-aldehyde at C1 (obscured in the ribofuranose configuration) to a hydroxymethyl group. In another aspect of the invention, the L-ribose thus formed is dehydroxylated at C2 to obtain 2-deoxy L-ribose.

In a preferred embodiment, L-Ribose is prepared from D-ribose by (a) forming a hydroxy-protected D-ribose; (b) reducing the hydroxy-protected D-ribose to a protected tetrol; (c) converting the tetrol to a tetraester, such as a tetraacetate; (d) hydrolyzing the protecting group to form a hydroxymethyl tetraester; (e) oxidizing the hydroxymethyl group to form a tetraester aldehyde; and (f) hydrolysing the ester groups to yield L-ribose.

In a second aspect of the invention, 2-deoxy-L-ribose is prepared by an extension of the approach described above. More particularly, L-ribose is methylated to form a methyl riboside, which is then perbenzoylated and anomerically acetylated, yielding a tetraester in essentially quantitative yield over the three operations. The tetraester is converted (at C1) to a β-selenophenyl ribofuranoside by treatment with phenylselenol and acid. Refluxing a solution of the β-selenophenyl ribofuranoside with an organotin compound (e.g., tributylstannane) and an initiator agent (e.g., AIBN) yields a tribenzoyl 2-deoxy-L-ribofuranoside, which is easily converted to 2-deoxy L-ribose by basic hydrolysis.

In a third aspect of the invention, L-arabinose is converted to 2-deoxy L-ribose. More particularly, perbenzoylation of L-arabinose followed by treatment with hydrogen bromide yields two isomers -- a pyranosyl bromide and a furanosyl bromide, which are separated by column chromatography. The pyranosyl bromide is reductively rearranged under Giese

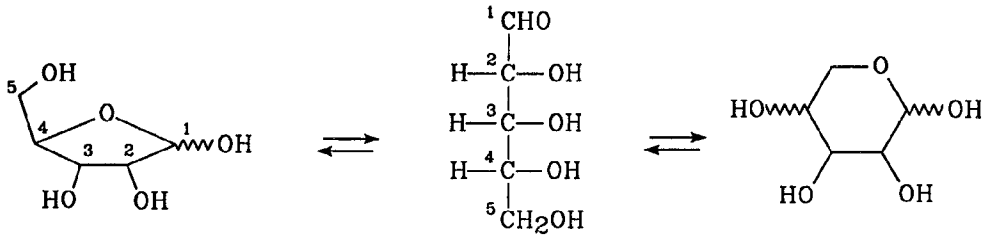
conditions, forming a perbenzoate of desired configuration, which is readily hydrolyzed to 2-deoxy L-ribose. In a fourth aspect of the invention, L-arabinose is converted to L-2-deoxyribose by an alternate route.

Detailed Description

In the discussion and synthetic schemes that follow, the following abbreviations are used:

Abbreviation	Explanation
TrCl	trityl chloride (triphenylmethyl chloride)
pyr	pyridine
Ac_2O	acetic anhydride
Ac	acetyl group
Et_2O	diethyl ether
DMSO	dimethyl sulfoxide
TFAA	trifluroacetic anhydride
Et_3N	triethylamine
EtOH	ethanol
MeOH	methanol
BzCl	benzoyl chloride
AcOH	acetic acid
Bz	benzoyl group
EtSH	ethyl mercaptan
PhSeH	phenylselenol
BF_3OEt_2	$(C_2H_5)_2OBF_3$
PhSe	phenylselenyl group
Bu_3SnH	tributylstannane (tributyltin hydride)
AIBN	2,2'-azobisisobutyronitrile
tol	toluene
Tol	toluoyl group

In solution, most carbohydrates exist in an equilibrium of several different conformations and configurations, with both cyclic and acyclic configurations being present. For example, "D-ribose" dissolves in water to form an equilibrium mixture of several species:

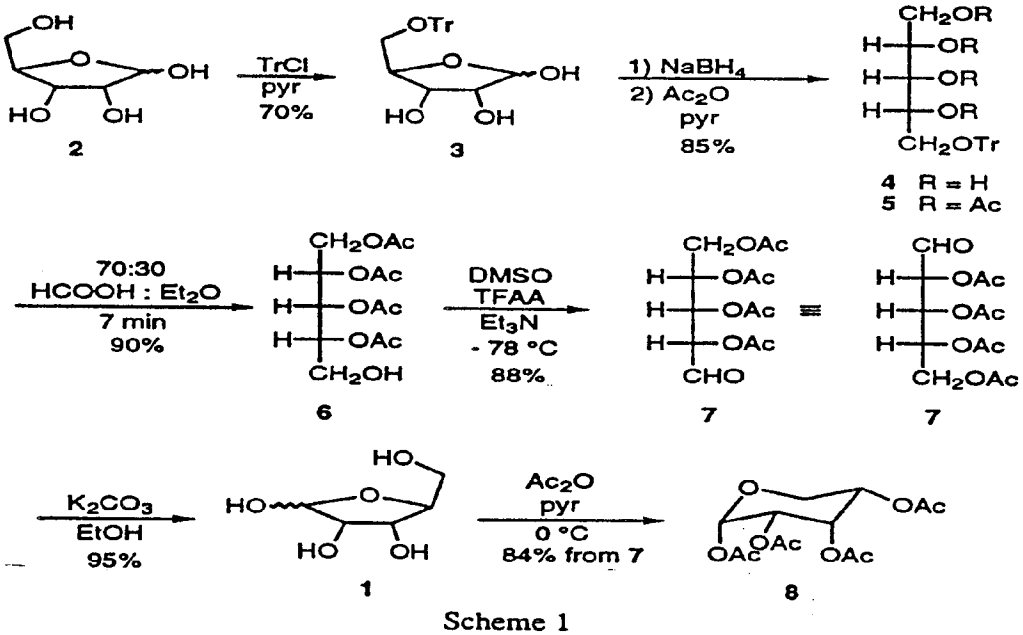


α- and β-D-ribofuranose D-ribose α- and β-D-ribopyranose

The α-and β-D-ribofuranose species are the predominant species in solution.

For convenience, the nomenclature "D-ribose" and "L-ribose" is used herein to denote both cyclic and acyclic species of the given sugar, unless a particular context indicates otherwise.

According to a first aspect of the invention, D-ribose is efficiently converted into L-ribose by interconversion of the two end groups of D-ribose -- the hydroxy group at C1 and the hydroxymethyl group at C5. In a preferred embodiment, the inter-conversion is accomplished via Synthetic Scheme 1.

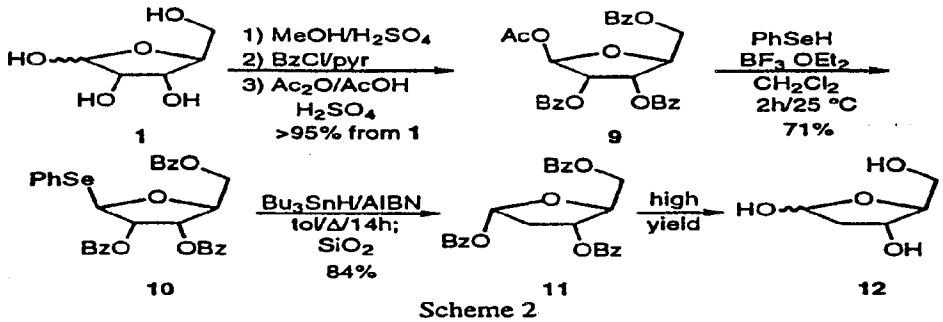


Scheme 1

In the first step of the synthesis, "D-ribose" **(2)** reacts as if it is primarily a furanose, and the hydroxymethyl group at C5 is protected with, e.g., a trityl group (See Kan, B.L. and Oppenheimer, N., J. Carbohydrate Research, 69, 308 (1979)). The trityl ribose **(3)** was prepared in 70% yield from D-ribose. Reduction of the aldehyde (in the open form of D-ribose) with a borohydride, such as sodium borohydride, cleanly furnished the tetrol **(4)**. Attempts at direct oxidations of the trityl ether of **(4)** in the presence of the alcohols, e.g., hydride abstraction with trityl salts, were generally unsuccessful. Therefore, the tetraacetate **(5)** was prepared by treatment of crude **(4)** with acetic anhydride and pyridine to give **(5)** in 85% yield from **(3)**. Hydrolysis of the trityl ether was carried out in 90% yield by treatment of **(5)** with a mixture of formic acid and diethyl ether for 7 minutes at 25°C. (See M. Bessodes, et al., Tetrahedron Letters, 27, 579 (1986).) In one embodiment, a 7:3 volume ratio of formic acid:diethyl ether was used. The alcohol **(6)** was isolated without any problems due to acetyl transfer. Several methods for oxidation of the hydroxy-methyl group to aldehyde were studied, but Swern oxidation turned out to give the highest yields. Addition of the alcohol **(6)** to a mixture of DMSO and trifluoroacetic anhydride (TFAA) in dichloromethane or other suitable solvent, followed by addition of a tertiary amine, such as Et_3N, at low temperature, (e.g. -78°C) furnished, after column chromatography, the aldehyde **(7)**, namely, L-ribose 2,3,4,5-tetraacetate, in 88% yield. Thus, this protected L-ribose derivative is available from D-ribose **(2)** in only five steps and 47% overall yield. L-ribose **(1)** itself was prepared in 95% yield by basic hydrolysis of **(7)** using, e.g., K_2CO_3 in EtOH. The steps of hydrolyzing the tritylether, Swern oxidation, and hydrolysis of the tetraacetate to yield L-ribose are all believed to occur with the open form of the sugar.

In order to prove the structure of the L-ribose **(1)**, we carried out its peracetylation to give the L-ribopyranose tetraacetate **(8)** in 84% overall yield from the aldehyde **(7)** (See H. Zinner, Chem. Ber. 86, 817 (1953). A rotation of -55.4° was reported for D-ribopyranose tetraacetate.) The optical rotation of **(8)** (+55.2°) matched that of D-ribopyranose tetraacetate but had the opposite sign, thus proving the structure and chirality of our synthetic material. Proton and carbon NMR for the compounds were consistent with the assigned structures. Thus, L-ribose **(1)** is available from D-ribose **(2)** in six steps in 39% overall yield.

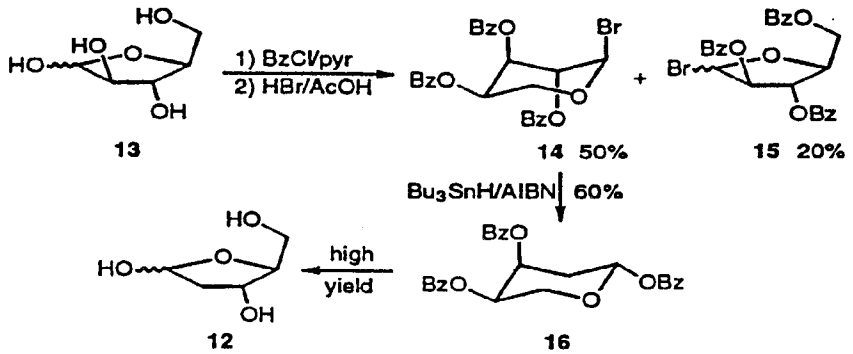
In a second aspect of the invention, 2-Deoxy L-ribose is prepared from L-ribose by an extension of the above-described route, depicted below in Scheme 2.



Scheme 2

Formation of the methyl riboside of L-ribose, followed by perbenzoylation and anomeric acetylation, afforded the tetraester **(9)** in essentially quantitative yield over the three operations. (See, e.g., Recondo, E.F.; Rinderknect, H., Helv. Chim. Acta 42, 1171 (1959).) Treatment with phenylselenol and acid gave the β-selenophenyl ribofuranoside **(10)** in 71% yield after column chromatography. As an alternative to phenylselenol, a mercaptan, such as phenyl mercaptan, or some other organo-chalcogen hydride or halide can be used, yeilding a β-substituted ribofuranoside. The method of Giese (Giese, B., et al., Liebigs Ann. Chem., 615 (1988)) was used to prepare the desired 2-deoxy carbohydrate. In general terms, this entailed refluxing **(10)** with a reducing agent and a free radical initiator, such as AIBN, benzoyl peroxide, or an azo initiator. More particularly, a solution of **(10)** was refluxed with tributylstannane (tributyltin hydride) and AIBN to furnish the tribenzoyl 2-deoxy-L-ribofuranoside **(11)** in 84% yield. (mp 111-3 °C; for D-isomer lit.mp 110-112 °C, 111 °C, 102 °C; $[\alpha]_D^{25}$ = -76°; for D-isomer lit. $[\alpha]_D^{25}$ = +75.3°, +78.0°,+77.3 °14). Basic hydrolysis of **(11)** is known to produce **(12)** in high yield. Thus 2-deoxy L-ribose **(12)** is available from L-ribose in five steps and nearly 60% overall yield.

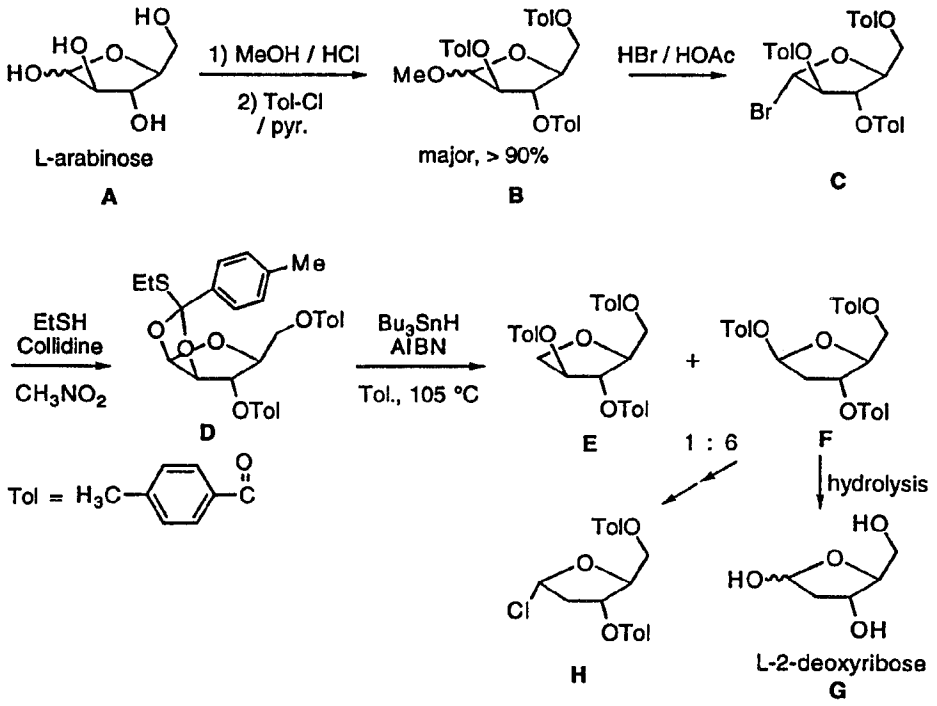
In a third aspect of the invention, an alternate efficient route to 2-deoxy L-ribose, beginning with readily available L-arabinose **(13)**, is provided. A preferred methodology is presented in Scheme 3.



Scheme 3

Formation of the perbenzoate using a benzoyl halide in pyridine or other suitable solvent (H.G. Fletcher, Jr., et al., J.American Chemical Society, 69, 1145 (1947)) and conversion to the anomeric bromide yielded the two isomers : a pyranosyl bromide **(14)** and a furanosyl bromide **(15)**, in 50% and 20% yield, respectively, after column chromatography. (See H.G. Fletcher, Jr. et al., J. American Chemical Society (1950) and R.K. Ness, et al., J. American Chemical Society (195), 80, 2007.) (Alternatively, chlorination with HCl can be used to form the anomeric chloride.) Reductive rearrangement of the pyranosyl bromide **(14)** under the conditions of Giese gave the expected product **(16)** in 60% yield ($[\alpha]_D^{25} = +213°$, for D-isomer lit.$[\alpha]_D^{25} = -195°$), which could be then hydrolyzed to 2-deoxy L-ribose **(12)** in good yield. Thus, inexpensive L-arabinose **(13)** can be converted into 2'-deoxy-L-ribose **(12)** in four steps and nearly 30% overall yield.

In still another aspect of the invention, L-Arabinoise is converted to L-2-deoxyribose by an alternate route, according to Scheme 4:



Scheme 4

L-Arabinose **A** was converted by known chemistry via the methyl tri-*O*-toluoylarabinofuranoside **B** into the α-tri-*O*-toluoylarabinofuranosyl bromide, ***C***. Treatment of this bromo triester ***C*** with ethanethiol and collidine in nitromethane (by the method of Balan, Bakinovskii, and Kochetkov) afforded the thioethyl orthoester, ***D***, namely, 1,2-((ethylthio)(4-methylphenyl)methylidene)-3,5-bis-*O*-(4-methylbenzoyl)arabinofuranose. Treatment of the thioethyl orthoester ***D*** with tributylstannane and AIBN in toluene at 105°C afforded the desired 2-deoxy 1,3,5-tri-*O*-toluoylarabinofuranose **F** as the major component of a 6:1 mixture with the 1-deoxyarabinose **E**. Hydrolysis of **F** afforded L-2-deoxyribose **G** in good yield. Alternatively **F** could be converted in one step and high yield into the crystalline α-anomer of the 3,5-bis-*O*-toluoylarabinofuranosyl chloride **H**, a known compound that has been taken on to the L-2'-deoxynucleosides by reaction with the anions of the appropriate bases. The chloride **H** can then be used to prepare β-nucleosides by known methods. (See e.g., Fujimori, S.; Iwanami, N.; Hashimoto, Y.; and Shudo, K. Nucleosides & Nucleotides **1992**, 11,341.)

It will be appreciated that the reactants, reagents, and methodologies of Schemes 1-4 can be modified in various ways without departing from the scope of the invention. For example, other acetyl-type halides (e.g., toluoyl bromide, benzoyl chloride, benzoyl bromide, etc.) can be used in place of toluoyl chloride. Chlorination with HCl is an alternative to bromination and formation of the bromo triester **C**. Weak hindered organic bases other than collidine, and short chain alkyl mercaptans (e.g., MeSH, EtSH, PrSH, etc.), can be used to convert the triester to a thioalkyl orthoester. Polar solvents, like acetonitrile, can be used in place of CH_3NO_2. Free radical initators like benzoyl peroxide, azo initators, and the like can be used instead of AIBN.

EXAMPLES

The following are nonlimiting examples of the synthetic routes provided by the present invention. In each case, Nuclear magnetic resonance spectra were taken on a Bruker AC200 spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane. All reactions involving moisture-sensitive reagents were performed in oven dried or flame dried glassware under a positive pressure of argon. Tetrahydrofuran and diethyl ether were distilled from Na-benzophenone ketyl radical. Dichloromethane, triethylamine, pyridine, dimethyl sulfoxide (DMSO), benzene, and toluene were distilled from CaH_2. Activation of powdered or pellet 4Å molecular sieves was done in a vacuum oven. All other reagents were obtained from Aldrich, Fisher, or Acros and used as received or purified using standard methods.

Thin layer chromatography was performed on Merck aluminum-backed silica gel 60 F_{254} (0.2 mm) precoated plates and was visualized using 254 nm ultraviolet light or by heating samples stained with p-anisaldehyde solution. Flash column chromatography was conducted on 230-400 mesh silca gel (SiO_2).

5-*O*-Trityl-D-ribose, (3) D-Ribose (8.0 g, 53.3 mmol) was azeotrope-distilled with benzene for 1 h, and then the benzene was completely distilled off. To the resulting slurry was added 50 mL of CaH_2-dried pyridine. The mixture was stirred until all the solid completely dissolved. Freshly recrystallized trityl chloride (16.4 g, 58.7 mmol) was added to the solution, and the reaction mixture was stirred at 25°C for 24 h. The pyridine was removed in vacuo, and further removed by coevaporation in vacuo with a toluene:ethanol mixture (4:1). The resulting slurry was taken up in water and extensively extracted with dichloromethane. The combined organic layers were shaken with brine, dried over $MgSO_4$, and the solvents removed in vacuo. The product was then purified by successive recrystallization from ethanol or recrystallization after a silica gel column to remove trityl alcohol to give the monotrityl ribose **(3)** (12.6 g, 60.2% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.1-7.2 (6H, m), 6.9-7.1 (9H, m), [5.1 (d, J = 4.2 Hz), 5.0 (s),lH total, mixture of α and β anomers], 3.9-4.1 (2H, m), 3.7-3.8 (1H, m), 2.9-3.2 (1H, m), 2.8-2.9 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.61, 143.50, 128.70, 128.61, 127.84, 127.65, 127.09 (2 C's), 96.76, 86.84, 83.01, 71.93, 71.64, 64.00.

5-*O*-Trityl-D-ribitol, (4) 5-*O*-Trityl-D-ribose **(3)** (12.6 g, 32 mmol) was dissolved in 25 mL of absolute ethanol and 100 mL of dry dichloromethane. To this solution was added 1.21 g (32 mmol) of $NaBH_4$ and the reaction mixture was stirred for 1 h at 25°C. Another 1.21 g of $NaBH_4$ was added and the reaction mixture stirred for another hour. The reaction was quenched by adding water and acetic acid to a pH of ~5-6, and then it was stirred for 5 min. This solution was then extracted with a large amount of dichloromethane. The combined organic layers were washed with 10 mL of water and then brine. It was dried over $MgSO_4$ and the solvents were removed in vacuo to give the polyol **(4)** (12.8 g, quant.). The crude product was used directly in the next step, except for a small portion that was purified by flash column chromatography and characterized spectroscopically. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.4-7.5 (6H, d, J = 7.0 Hz), 7.2-7.4 (9H, m), 4.98 (lH, d, J = 5.4 Hz), 4.60 (lH; d, J = 3.7 Hz), 4.52 (lH, d, J = 4.6 Hz), 4.39 (1H, t, J = 5.1 Hz), 3.89 (1H, m), 3.25-3.6 (H., m), 3.0-3.2 (2H, m). ^{13}C NMR (50 MHz, DMSO): δ 144.42, 128.68, 127.90, 126.99, 85.90, 73.29, 72.78, 71.74, 65.98, 63.25.

5-*O*-Trityl-D-ribitol tetraacetate, (5) The crude 5-*O*-trityl-D-ribitol, **(4)** (12.8 g, 32 mmol) was dissolved in 160 mL of dry pyridine and 30 mL (321 mmol)of acetic anhydride. After the solution stirred for 24 h at 25 °C, most of the pyridine was removed in vacuo (but not completely so that some was still present to neutralize the acetic acid formed by hydrolysis of the excess acetic anhydride). The resulting mixture was taken up in water and extracted extensively with dichloromethane. The organic layer was rinsed with brine and dried over $MgSO_4$. The solvents were removed in vacuo, and pyridine was further remove by coevaporation with a mixture of toluene and ethanol, to give the crude peracetate **(5)** (18.5 g, >100%, which was pure enough to be used directly in the next step). The peracetate **(5)** can be purified by flash column chromatography (ethyl acetate/hexanes) to give 15.3 g (85% from 3). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3-7.45 (6H, m), 7.1-7.3 (9H, m), 5.43 (1H, dd, J = 6.2, 4.8 Hz), 5.2-5.3 (2H, m), 4.30 (1H, dd, J = 12.0, 3.3 Hz), 4.09 (1H, dd, J = 12.0, 6.9 Hz), 3.28 (1H, dd, J = 10.4, 3.2 Hz), 3.11 (1H, dd, J = 10.4, 5.5 Hz), 2.14 (3H, s), 2.00 (3H, s), 1.92 (3H, s), 1.88 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.40, 169.74, 169.59, 169.07, 143.36, 128.48, 127.73, 127.01, 86.59, 70.78, 69.70, 69.32, 61.81, 20.84, 20.63, 20.53, 20.45 (one highfield carbon not resolved).

D-Ribitol, 1,2,3,4-tetraacetate,(6) The crude 5-*O*-trityl-D-ribitol tetraacetate, **(5)** (18.5 g, 32 mmol) was placed in a 250 mL round bottom flask. To this flask was added a mixture of 140 mL of formic acid, 55 mL of ether, and 5 mL of water. The flask was hand shaken for 7.5 min at which time the contents were poured into a large amount of dichloromethane. Water was added and the layers separated. The aqueous layer was successively extracted with a large amount of dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate solution until neutral and then rinsed with brine and dried over $MgSO_4$. Removal of the solvents in vacuo afforded the alcohol **(6)** (12.5 g, 67% from **3**). This crude material was used in the next step directly. However, beginning with a pure sample of **5**, the yield of **6** was 90%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.21-5.32 (2H, m), 4.96-5.04 (1H, m), 4.27 (1H, dd, J = 12.3, 3.2 Hz), 4.05 (1H, dd, J = 12.8, 6.4 Hz), 3.77 (1H, dd, J = 12.6, 3.7 Hz), 3.61 (1H, dd, J = 12.6, 5.3 Hz), 2.06 (3H, s), 2.03 (3H, s), 2.02 (3H, s), 1.98 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.54, 170.26, 170.02, 169.75, 81.83, 72.45, 69.72, 61.80, 60.75, 20.78, 20.69, 20.53 (one highfield carbon not resolved).

L-ribose, 2,3,4,5-tetraacetate, (7) To a solution of trifliuoroacetic anhydride (0.211 mL, 1.50 mmol) in 2 mL of dichloromethane cooled to -78 °C was added dropwise a solution of dimethylsulfoxide(DMSO) (141 mL, 2.0 mmol) in 2 mL of dichloromethane. After the mixture was stirred for 10 min, a solution of D-ribitol, 1,2,3,4-tetraacetate **(6)** (0.58 g, 1.8 mmol) in 3 mL of dichloromethane was added dropwise at -78 °C. The temperature of the

solution was carefully maintained below -70°C during the additions. The reaction mixture was stirred for 5 min at -78°C and then allowed to warm up to 25°C briefly. It was then cooled again to -78°C and 2.87 mL of triethylamine was added dropwise. After stirring for 15 min. at -78°C, the reaction mixture was warmed up to 25°C and quenched with water. Acetic acid was added to neutralize the solution. Water was added, the layers separated, and the aqueous layer extracted with dichloromethane. The residue obtained after drying over $MgSO_4$ and evaporation of the solvents in vacuo was purified by flash column chromatography (ethyl acetate/hexanes) to give the aldehyde **(7)** (0.28 g, 88%). Recrystallized from dichloromethane and hexanes gave 7 with mp:105.5-107°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.37 (1H, s), 5.48 (1H, dd, J = 8.9, 2.4 Hz), 5.32 (1H, d, J = 2.4 Hz), 5.13-5.21 (1H, m), 5.23 (1H, dd, J = 12.6, 2.5 Hz), 4.04, (1H, dd, J = 12.6, 4.2 Hz), 2.06 (3H, s), 1.97 (3H, s), 1.94 (3H, s), 1.88 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 192.84, 170.37, 169.91, 169.32, 168.92, 76.59, 68.17, 61.29. 20.56 (2 C's), 20.29 (two highfield carbons not resolved).

L-Ribose, (1) L-Ribose, 2,3,4,5-tetraacetate **(7)** (71 mg, 0.223 mmol) was stirred with potassium carbonate (138 mg, 1.00 mmol) in 4 mL of ethanol and 1 drop (33 mg, 1.83 mmol) of water. After 4 h, the reaction was complete (by TLC). The potassium carbonate was filtered off and the ethanol was removed in vacuo to give L-ribose **(1)** (32 mg, 95%, 84% from 6). For proof of structure, the L-ribose was characterized as its pyranosyl tetraacetate **(8)**.

β-L-Ribopyranose tetraacetate, (8) The solution of the L-ribose **(1)** isolated from the hydrolysis of 71 mg of L-ribose-2,3,4,5-tetraacetate **(7)** in 1 mL of pyridine and 1 mL of acetic anhydride was allowed to sit at +4°C for 1 day. The solution was then poured onto ice and conc. HCl was added until a pH of ~ 2-3 was obtained. Water was added, the layers separated, and the aqueous layer extracted with dichloromethane. Drying over $MgSO_4$ and evaporation of the solvents in vacuo afforded the crude tetraacetate **(8)** (60 mg, 84%) which was shown by ^{1}H NMR to be a mixture of isomers of ribose tetraacetates. Recrystallization of this material from methanol at -10°C afforded 15 mg of β-L-ribopyranose tetraacetate **(8)** with mp: 116-8°C. ^{1}H NMR (200 Mhz, $CDCl_3$): δ 6.03 (1H, d, J = 4.8 Hz), 5.48 (1H, t, J = 3.3 Hz), 5.12-5.18 (1H, m), 5.04 (1H, t, J = 4.1 Hz), 4.03 (1H, dd, J = 12.3, 3.4 Hz), 3.90 (1H, dd, J = 12.3, 5.6 Hz), 2.14, 2.11, 2.10, 2.09 (overlapping singlets, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.66, 169.54, 169.25, 168.54, 90.74, 67.12, 65.97 (2 C's), 62.49, 20.63, 20.56, 20.44 (one highfield carbon not resolved). $[\alpha]_D^{25} = +55.2°$

β-D-Ribopyranose, tetraacetate The reaction of D-ribose (5 g), acetic anhydride (20 mL) and pyridine (20 mL) afforded 4.5 g (42%) of the β-D-ribopyranose, tetraacetate after recrystallization. This compound had ^1H and ^{13}C NMR's which were superimposable with those of the L-isomer and an identical optical rotation but of the opposite sign.

Methyl L-ribofuranoside Five drops of fuming sulfuric acid was added to a solution of L-ribose **(1)** (30 mg, 0.2 mmol) in 10 mL of anhydrous methanol. The mixture was stored in a refrigerator for 24 h, and TLC indicated completion of the reaction. The reaction mixture was then passed through a strongly basic Dowex ion-exchange column, and the column was thoroughly rinsed with more methanol. Rotary evaporation and co-evaporation with toluene gave crude product (33 mg, 0.2 mmol, 100%) that was directly used in the next reaction. ^1H NMR (200 MHz, MeOD): δ 4.75 (1H, s, H1), 4.06-3.85 (3H, m, H2,3,4), 3.72 (1H, dd, J = 11.6, 3.3 Hz, H5), 3.54 (1H, dd, J = 11.8, 6.2 Hz, H5'). ^{13}C NMR (50 MHz, MeOD): δ 109.65, 84.66, 75.97, 72.48, 64.80, 55.20.

Methyl 2,3,5-tri-*O*-benzoyl-β-L-ribofuranoside A solution of methyl L-ribofuranoside (33 mg, 0.2 mmol) and 0.15 mg of benzoyl chloride in 2 mL of pyridine was left at 25°C overnight. The reaction was then quenched with 20 mL of water. The mixture was extracted three times with chloroform. The combined chloroform layer was rinsed with water and brine, dried over $MgSO_4$, and the solvent removed in vacuo. Co-evaporation with toluene afforded the product (100 mg, 0.2 mmol, 100%) as a syrup which was used in the next reaction directly. ^1H NMR (200 MHz, $CDCl_3$): δ 8.12-7.25 (15H, m), 5.88 (1H, dd, J = 6.6, 4.8 Hz, H3), 5.68 (1H, d, J = 4.8 Hz, H2), 5.15 (1H, s, Hl), 4.75-4.64 (2H, m, H4, H5), 4.52 (1H, dd, J = 2.8, 6.3 Hz, H5'), 3.42 (3H, s, CH_3).

Acetyl 2,3,5-tri-*O*-benzoyl-L-ribofuranoside, (9) To a mixture of methyl 2,3,5-tri-*O*-benzoyl-β-L-ribofuranoside (100 mg, 0.2 mmol), 1 mL of acetic anhydride and 2 mL of acetyl chloride was added 3 drops of concentrated sulfuric acid. The mixture turned dark immediately, and was stored at -10°C overnight. The solution was then poured onto excess sodium bicarbonate and ice. The aqueous layer was extracted with dichloromethane. The organic layer was then washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the tetraester **(9)** (100 mg, 0.198 mmol, 99%) was isolated. It was shown by NMR to be pure enough to be used directly in the next reaction. ^1H NMR (200 MHz, $CDCl_3$): δ (mixture of α and β forms): 8.2-7.8 (6H, m), 7.6-7.2 (9H, m), 6.72 (0.44H, d, J = 4.5 Hz, H1), 6.44 (0.56H, s, H1), 6.0-5.6 (2H, m), 4.9-4.4 (3H, m), 2.15 (1.3H, s, CH_3), 2.00 (1.7H, s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.0, 165.2, 165.0,

133.5, 133.4, 133.2, 129.8, 129.7, 128.5, 128.4, 98.2, 94.3, 82.1, 79.9, 75.0, 71.2, 71.1, 70.7, 64.0, 63.9, 20.9, 20.8 (it was very difficult to pick out all of the peaks in this mixture).

Phenyl 2,3,5-tri-*O*-benzoyl-L-selenoribofuranoside, (10) Acetyl 2,3,5-tri-*O*-benzoyl-L-ribofuranoside, 9 (100 mg, 0.198 mmol), 33.8 mL of benzeneselenol, and 23.4 µl of boron trifluoride etherate were stirred in 2 mL of dry 1,2-dichloromethane at 25°C for 2 h until TLC indicated that the reaction was complete. Excess sodium bicarbonate solution was added and the aqueous layer was extracted with dichloromethane. The organic layer was then washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by flash column chromatography (hexanes/ethyl acetate gradient elution 0 - 20%) to give the phenylseleno compound **(10)** (85 mg, 71.4%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10-8.00 (6H, m), 7.87 (2H, d, J = 8.74 Hz), 7.62-7.28 (12H, m), 5.89 (lH, dd, J = 6.6, 4.8 Hz, H3), 5.67 (1H, d, J = 4.8 Hz, H2), 5.26 (1H, s, Hl), 4.80-4.67 (2H, m, H4, H5), 4.52 (lH, dd, J = 12.8, 6.5 Hz, H5').

2-Deoxy-l,3,5-tri-*O*-benzoyl-L-α-ribofuranose, (11) A solution of 1.8 mg of AIBN and 41 mL of tributyltin hydride in 1 mL of dry toluene was added via syringe pump to a solution of phenyl 2,3,5-tri-*O*-benzoyl-L-selenoribofuranoside **(10)** (65 mg, 0.108 mmol) in 10 mL of dry toluene at 105°C over 5 h. The reaction mixture was then heated at the same temperature overnight. After evaporation of the solvent, the residue was separated by flash column chromatography to give the 2-deoxyribofuranoside **(11)** (41 mg, 85%). Recrystallization from hexanes/ether gave pure **(11)** (32 mg, 66%) with mp 111 - 113°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11-8.0 (6H, m), 7.61-7.3 (9H, m), 6.78 (1H, d, J = 4.4 Hz, Hl), 5.64 (br d, 1H, J = 6.6 Hz, H3), 4.82 (1H, m, J = 2.0 Hz, H4), 4.63 (2H, m, H5, H5'), 2.64 (1H, ddd, J = 14.9, 6.5, 4.8 Hz, H2), 2.50 (1H, d, J = 14.9 Hz, H2'). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.06, 165.49, 133.41, 133.24, 129.79, 129.73, 129.62, 129.50, 128.42, 128.29, 99.06, 84.19, 74.66, 64.23, 38.77 (several lowfield carbons not resolved).

1,2,3,4-Tetra-*O*-benzoyl-L-arabinopyranose Benzoyl chloride (10 mL) was added to a solution of arabinose **(13)** (3g, 20 mmol) in 20 mL of pyridine at 0°C. The reaction mixture was allowed to warm to 25°C and stirred overnight. It was then poured onto ice and extracted with chloroform. Pyridine in the organic layer was removed by washing with water following by washing with 0.1 M sulfuric acid. Evaporation of the solvent resulted in 17.3 g (150%) of mixture that consists of the α and β forms of both the arabinopyranose and arabinofuranose perbenzoates.

1

1-α-Bromo-l-deoxy-2,3,4-tri-*O*-benzoyl-L-arabinopyranose, (14) The above mixture of arabinofuranose and arabinopyranose perbenzoates (8.6 g) was mixed with 6 mL of anhydrous 1,2-dichloroethane and 12 mL of 30% HBr in acetic acid. The mixture was stirred at 25 °C for 5 h and was then poured onto ice water. After extraction with dichloromethane, the organic layer was washed with water, saturated sodium bicarbonate solution and brine. After drying over $MgSO_4$, the solvents were removed in vacuo. Several attempts to recrystallize the product failed. Flash column chromatography on silica gel (gradient ethyl acetate/hexanes 10-35%) afforded two fractions. The first fraction was the desired glycosyl bromide **(14)** (2.6 g, 50% from **13**). The second fraction (1.1 g, 21%) was the corresponding furanosyl bromide. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12-7.83 (6H, m), 7.7-7.2 (9H, m), 6.94 (1H, d, J = 3.8 Hz, H1), 6.15 (1H, dd, J = 10.4, 3.4 Hz, H3), 5.85 - 5.83 (1H, m, H4), 5.72 (1H, dd, J = 10.4, 3.8 Hz, H2), 4.48 (1H, d, J = 13.2 Hz, H5), 4.23 (lH, dd, J = 13.5, 1.7 Hz, H5'). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.51,165.48, 165.36, 133.68, 133.56, 133.32, 130.51, 129.95, 129.82, 129.68, 129.20, 128.88, 128.58, 128.50, 128.31, 89.77, 68.85, 68.64, 68.51, 64.96.

2-Deoxy-α-l,3,4-tri-*O*-benzoyl-L-ribopyranose, (16) The α-arabinopyranosyl bromide **14** (0.525 g, 1 mmol) was stirred in 60 mL of toluene under argon at 105 °C. A solution of 350 µL (1.3 mmol) of tributyltin hydride and 16.4 mg (0.1 mmol) of AIBN in 4 mL of toluene was added via syringe pump over 6 h. The mixture was then heated at 100 °C for an additional 18 h. After evaporation of the solvent, the resulting syrup was purified by flash column chromatography on silica gel (gradient ethyl acetate/hexanes 10-20%) to give the desired product **15** (270 mg, 61%) which could be further purified by recrystallization from refluxing ether/hexanes. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.15-8.08 (h., m), 7.94 (2H, dd, J = 8.7, 1.5 Hz), 7.62 - 7.3 (9H, m), 6.67 (1H, br s, H1), 5.83 (1H, ddd, J = 11.8, 4.8, 3.1 Hz, H3), 5.69 (1H, br s, H4), 4.32 (1H, dd, J = 13.1, 1.0 Hz, H5), 4.16 (1H, dd, J = 13.1, 2.5 Hz, H5'), 2.66 (1H, ddd, J = 13.1, 11.8, 3.4 Hz, H2), 2.36 (1H, dd, J = 13.1, 4.8 Hz, H2'). ^{13}C NMR (50 Mhz, $CDCl_3$): δ 165.73, 165.55, 164.76, 133.53, 133.28, 133.20, 129.80, 129.74, 129.62, 129.46, 128.55, 128.45, 128.33, 92.46, 67.92, 66.27, 63.33, 30.29 (two lowfield carbons not resolved).

1-*O*-Methyl-2,3,5-tri-*O*-*p*-toluoy-L-arabinofuranose, (B) L-arabinose (5g) was dried by co-evaporating with toluene under vacuum. Methanol (100 ml) and 15% HC1 in methanol (15 ml) were added and the mixture was stirred at 25 °C for two hours. The solution of L-arabinose was then complete. The flask was let sit in a refrigerator over night. Methanol and HCl were then evaporated under vacuum. The residue was co-evaporated with pyridine twice to remove any trace of methanol. The residue was dissolved in pyridine (50 ml) and toluoyl

chloride (15.4 ml) was added with ice cooling. The mixture was then stirred at 25 °C for 2 hours and refrigerated overnight. Water was then added to quench the reaction. Pyridine and water were evaporated under vacuum. The residue was then dissolved in 95% ethanol and excess K_2CO_3 dded to hydrolyze toluoyl anhydride. As soon as the hydrolysis was complete (about 20 minutes), ethanol was removed by roto-evaporation. The residue was dissolved in 300 ml of methylene chloride and extracted with 2 x 100 ml of 1 N sulfuric acid, then 100 ml of water, and 100 ml of 1 N K_2CO_3, 100 ml of water, and finally saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and roto-evaporated to give a slurry of 18.15 g (105%). Crude NMR showed very little of pyridine or toluoyl chloride. Less than 10% of the mixture were arabipyranoses. The rest was a 3: 1 mixture of α- and β-arabifuranose. The crude product was taken on to the next reaction. A small sample was chromatographed. Although the furanoses could be separated from the pyranoses, the α-arabifuranose and β-arabifuranose were inseparable. ^1H ($CDC1_3$): 7.8-8.0 (m, 6H), 7.0-7.3 (m, 6H), 5.95 (dd, 1/4 H, J = 6.9, 5.3 Hz), 5.56 (d, 3/4 H, J = 5.0 Hz), 5.50 (s, 1H), 5.34 (d, 1/4 H, J = 4.5 Hz), 5.17 (s, 3/4 H), 4.4-4.9 (m, 3H), 3.49 (s, 9/4 H), 3.37 (s, 3/4 H), 2.36-2.40 (singlets, 9H), ^{13}C ($CDC1_3$): 166.29, 166.03, 165.97, 165.89, 165.55, 144.32, 144.27, 144.19, 143.60, 130.03, 129.97, 129.93, 129.85, 129.20, 129.05, 127.26, 127.15, 126.52, 126.46, 107.02, 101.50, 82.09, 81.11, 78.93, 77.91, 77.58, 76.38, 65.81, 63.68, 55.52, 54.98, 21.72, 21.66.

2,3,5-Tri-*O*-*p*-toluoyl-α-L-arabifuranosyl bromide, (C) Crude 1-O-methyl-2,3,5-tri-O-toluoyl-L-arabinofuranose (4 g) was dissolved in minimum amount of methylene chloride, and 20 ml of 30% w/w HBr in acetic acid was added. The reaction mixture was stirred at 25 °C for 30 minutes and then diluted with 150 ml of methylene chloride. The solution was then extracted with 50 ml portions of saturated $NaHCO_3$ till the aqueous layer was basic. The organic layer was then washed with brine and dried over $MgSO_4$. Methylene chloride was evaporated under vacuum. The product was then recrystallized in dry ether and hexanes to give thin needles (2.8 g, 67% from arabinose). m.p.: 120-121 °C. 1H ($CDC1_3$): 8.03 (d, 2H, J = 8.2 Hz), 7.92 (d, 2H, J = 8.2 Hz), 7.83 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 7.15 (d, 2H, J = 8.2 Hz), 7.08 (d, 2H, J = 8.1 Hz), 6.63 (s, 1H, H1), 5.93 (s, 1H, H2), 5.60 (d, 1H, J = 3.6 Hz, H3), 4.68-4.94 (m 3H, H4, H5), 2.42 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H). ^{13}C ($CDC1_3$): 166.12, 165.79, 165.18, 144.68, 144.61, 143.82, 130.14, 130.05, 129.89, 129.37, 129.31, 129.12, 126.84, 126.10, 125.78, 88.83, 85.59, 84.86, 76.64, 62.55, 21.79, 21.79 (two C overlap), 21.70. IR:

1,2-*O*-[Ethylthio-(4-methylphenyl)-methylidene]-3,5-di-*O*-toluoylarabifuranose, (D) (The method of "Balan, N. F.; Bakinovskii, L. V.; and Kochetkov, N. K. Bioorg. Khim, 1980, 6, 1657." was used.)The bromide (0.567 g) was dissolved in 4 ml of dry nitromethane.

Collidine (158 ul) and ethanethiol (100 ul) were added, and the mixture was stirred at 25 °C for 30 minutes. The reaction was taken up in 70 ml of methylene chloride and washed with water for three times (70 ml total). The organic layer was then washed with brine, dried over $MgSO_4$ and roto-evaporated to give white solid residue (0.56 g). Recrystallization in ether and hexanes then gave the pure product (0.38 g, 70%). m.p.: 74 - 76 °C. ^1H ($CDCl_3$): 7.93 (d, 2H, J = 8.2 Hz), 7.91 (d, 2H, J = 8.2 Hz), 7.57 (d, 2H, J = 8.1 Hz), 7.15-7.30 (m, 6H), 6.35 (d, 1H, J = 4.1 Hz, H1), 5.56 (s, 1H, H3), 5.16 (d, 1H, J = 4.2 Hz, H2), 4.61 (t, 1H, J = 7.1 Hz, H4), 4.22 (d, 2H, J = 7.2 Hz, H5), 2.42 (s, 3H), 2.39 (s, 3H), 2.37 (q, 2H, J = 7.4 Hz), 2.36 (s, 3H), 1.08 (t, 3H, J = 7.4 Hz), ^{13}C ($CDCl_3$): 165.89, 165.35, 144.49, 143.70, 138.97, 136.14, 129.92, 129.84, 129.26, 129.06, 128.79, 127.06, 126.34, 125.81, 119.95, 107.28, 85.22, 84.70, 77.61, 63.60, 24.69, 21.74, 21.67, 21.29, 14.47.

2-Deoxy-l,3,5-tri-*O-p*-toluoyl-α-L-*erythro*-pentofuranose, (F) 1,2-O-[Ethylthio-(4-methylphenyl)-methylidene]-3,5-di-O-toluoylarabifuranose (0.11 g) was dissolved in 15 ml of dry toluene and heated at 105 °C. A solution of AIBN (8.2 mg) and Bu_3SnH (108 ul) in 10 ml of dry toluene was added via syringe pump over 4 hours. The solution was heated for another one hour after the addition was complete. The toluene was roto-evaporated, and the residue was dissolved in acetonitrile (75 ml).The solution was extracted three times with pentane (total 75 ml) to remove the non-polar tin residue. The acetonitrile layer was then concentrated under vacuum. Recrystallization in ether and pentane furnished the pure product as thin needles (75 mg, 75%). Alternatively, the crude product can be worked up by the method of (Crich D. and Sun S. J. Org. Chem. 1996, 61, 7200.) to get a completely tin-free product. mp: 105-107°C (lit. 107 °C for D-isomer, "Seela, F.; Steker, H.; Driller, H.; Bindig, U. Liebigs Ann. Che~ 1987, 15.). ^1H ($CDCl_3$): 7.94 (d, 2H, J = 8.4 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.1 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.1 Hz), 7.11 (d, 2H, J = 8.1 Hz), 6.74 (dd, 1H, J = 5.6, 2.4 Hz, H1), 5.73 (ddd, 1H, J = 7.1, 4.8, 2.8 Hz, H3), 4.47-4.77 (m, 3H, H4, H5), 2.85 (ddd, 1H, J = 14.4, 7.0, 2.4 Hz, H2), 2.62 (dt, 1H, J = 14.4, 5.4 Hz, H2'), 2.41, 2.39, 2.36 (three singlets, 9H), ^{13}C ($CDCl_3$): 166.21, 166.09, 165.60, 144.29, 144.06, 143.74, 129.85, 129.82, 129.82 (two C overlap), 129.24, 129.16, 129.06, 126.96, 126.92, 126.67, 99.04, 82.94, 74.58, 64.43, 38.81, 21.72, 21.67 (one high field carbon not resolved).

2-Deoxy-3,5.di-*O-p*-Toluoyl-a-L-*erythro*-pentofuranosyl chloride, (H) To a solution of 2-Deoxy-1,3,5-tri-*O-p*-toluoyl-α-L-*erythro*-pentofuranose (1.7 g) dissolved in a minimum amount of glacial acetic acid was added 15% HC1 in acetic acid (3.5 ml, prepared according to "Rolland, V.; Kotera M.; and Lhomme J. ***Synth Comm.* 1997,** 27, 3505." by adding water to acetyl chloride.) The solution was shaken at 25 °C for 20 minutes whereupon a thick

crystalline mass precipitated. The crystals were filtered off and quickly rinsed with acetic acid (1 ml) and then ether and hexanes, dried under high vacuum. Yield 0.95 g, 70%. mp: 109.5 - 111 °C. ^{1}H ($CDC1_3$): 8.00 (d, 2H, J = 8.2 Hz), 7.90 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 7.24 (d, 2H, J = 8.2 Hz), 6.48 (d, 1H, J = 4.7 Hz, H1), 5.55-5.59 (m, 1H, H3), 4.83-4.89 (m, 1H, H4), 4.54-4.73 (m, 2H, H5), 2.70-2.87 (m, 2H, H2), 2.43 (s, 3H), 2.42 (s, 3H). ^{13}C ($CDC1_3$):

The invention has been described in preferred and exemplary embodiments, but is not limited thereto. A variety of modifications, modes of operation and embodiments--all within the ability and skill of those skilled in the art--can be made without the exercise of further inventive activity.

All references cited herein are incorporated by reference as if set forth in their entirety.

WHAT IS CLAIMED IS:

1. A method for converting D-ribose into L-ribose or 2-deoxy L-ribose, comprising:

interconverting D-ribose's C1 hydroxy group and C5 hydroxymethyl group, and optionally, dehydroxylating the L-ribose thus formed to obtain 2-deoxy L-ribose.

2. A method as recited in claim 1, wherein D-ribose is converted to L-ribose by forming an aldehyde at C1 and reducing the aldehyde or its pseudo-aldehyde equivalent to obtain L-ribose.

3. A method as recited in claim 1, wherein D-ribose is converted to L-ribose by the following steps:

(a) forming a hydroxy-protected D-ribose, having a protected hydroxy group at C5;

(b) reducing the hydroxy-protected D-ribose to a protected tetrol;

(c) esterifying the protected tetrol to a tetraester;

(d) forming a hydroxymethyl tetraester by deprotecting the protected hydroxy group;

(e) oxidizing the hydroxymethyl tetraester to a tetraester aldehyde; and

(f) hydrolysing the tetraester aldehyde to yield L-ribose.

4. A method as recited in claim 3, wherein the C5 hydroxy group is protected with a trityl group.

5. A method as recited in claim 3, wherein the hydroxy-protected D-ribose is reduced using a borohydride reagent.

6. A method as recited in claim 5, wherein the borohydride reagent is sodium borohydride.

7. A method as recited in claim 3, wherein the tetraester is a tetraacetate.

8. A method as recited in claim 3, wherein the tetraacetate is formed by treating the protected tetrol with acetic acid and pyridine.

9. A method as recited in claim 3, wherein the hydroxymethyl tetraester is formed by hydrolyzing the tetraester.

10. A method as recited in claim 9, wherein a mixture of formic acid and ether is used to hydrolyze the tetraester.

11. A method as recited in claim 10, wherein the mixture is a 7:3 parts by volume mixture of formic acid and diethyl ether.

12. A method as recited in claim 3, wherein the hydroxymethyl tetraester is oxidized to a tetraester aldehyde using Swern oxidation.

13. A method as recited in claim 12, wherein Swern oxidation proceeds by addition of the hydroxymethyl tetraester to a mixture of DMSO and trifluoroacetic anhydride in a solvent, followed by addition of a tertiary amine.

14. A method as recited in claim 13, wherein the tertiary amine is triethylamine.

15. A method as recited in claim 3, wherein the tetraester aldehyde is isolated using column chromatography.

16. A method as recited in claim 3, wherein the tetraester aldehyde is hydrolyzed to L-ribose using ethanolic base.

17. A method as recited in claim 15, wherein the ethanolic base comprises a solution of potassium carbonate in ethanol.

18. A method as recited in Claim 1, wherein L-ribose is converted to 2-deoxy L-ribose by the following steps:

(a) forming a methyl riboside of L-ribose;

(b) forming a tetraester from the methyl riboside by benzoylation and anomeric acetylation;

(c) treating the tetraester with phenylselenol or phenyl mercaptan and acid to obtain a β-substituted ribofuranoside;

(d) refluxing the β-substituted ribofuranoside with an organotin hydride and an initiator to obtain a tribenzoyl 2-deoxy-L-ribofuranoside; and

(e) hydrolyzing the tribenzoyl 2-deoxy-L-ribofuranoside to obtain 2-deoxy L-ribose.

19. A method as recited in claim 18, wherein the methyl riboside is formed by treating the L-ribose with methanol and acid.

20. A method as recited in claim 18, wherein the organotin hydride comprises tributyltin hydride.

21. A method as recited in claim 18, wherein the initiator comprises AIBN.

22. A method for converting L-arabinose into 2-deoxy L-ribose, comprising:

(a) treating L-arabinose with a benzoyl halide to yield arabinopyranose perbenzoate;

(b) treating the arabinopyranose perbenzoate with hydrogen bromide to yield a pyranosyl bromide;

(c) converting the pyranosyl bromide to a 2-deoxy-tribenzoyl-ribopyranose by reductive rearrangement; and

(d) hydrolyzing the 2-deoxy-tribenzoyl-ribopyranose to yield 2-deoxy-L-ribose.

23. A method as recited in claim 22, wherein the reductive rearrangement is carried out with an organotin hydride and a reducing agent.

24. A method as recited in claim 23, wherein the organotin hydride comprises tributyltin hydride.

25. A method as recited in claim 23, wherein the reducing agent comprises AIBN.

26. A method as recited in claim 22, further comprising the step of isolating the pyranosyl bromide using column chromatography.

27. A method for converting L-arabinose into 2-deoxy L-arabinose, comprising:

(a) treating L-arabinose with a toluoyl or benzoyl halide to yield a tri-*O*-(toluoyl or benzoyl) arabinofuranoside;

(b) treating the tri-*O*-(toluoyl or benzoyl) arabinofuranoside with hydrogen bromide or hydrogen chloride to yield a bromo- or chloro-triester;

(c) treating the triester with an alkyl mercaptan and a weak hindered organic base to yield a thioalkyl orthoester;

(d) reducing the thioalkyl orthoester to a 2-deoxy 1, 3, 5-tri-*O*-(toluoyl or benzoyl) arabinofuranose; and

(e) hydrolyzing the 2-deoxy 1, 3, 5-tri-*O*-(toluoyl or benzoyl) arabinofuranose to yield 2-deoxy L-ribose.

28. A method as recited in claim 27, wherein the weak hindered organic base comprises collidine.

29. A method as recited in claim 27, wherein the alkyl mercaptan comprises methyl, ethyl or propyl mercaptan.

30. A method as recited in claim 27, wherein the thioalkyl orthoester is reduced with an organic tin hydride.

31. A method as recited in claim 30, wherein the organic tin hydride is tributyltin hydride.

32. A method as recited in claim 27, wherein the thioalkyl orthoester is reduced in the presence of an initiator.

33. A method as recited in claim 32, wherein the initiator comprises AIBN.

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(54) Title: SYNTHESIS OF L–RIBOSE AND 2–DEOXY L–RIBOSE

(57) Abstract

A method for synthesizing L–ribose (1) and 2–deoxy L–ribose (12) from inexpensive D–ribose (2) is provided. The 5–*O*–trityl ribose (3) (prepared in 70 % yield from D–ribose) is reduced with borohydride to give the tetrol (4), which is then peracetylated to the tetraacetate (5). Hydrolysis of the trityl ether followed by Swern oxidation affords the aldehyde (7) via the alcohol (6). This aldehyde is a protected form of L–ribose, being L–ribose 2,3,4,5,–tetraacetate. Mild basic hydrolysis of the acetate affords L–ribose itself (1), thus ending an efficient six–step synthesis of (1) from (2) which proceeds in 39 % overall yield. In a second aspect of the invention, L–ribose is converted into the β–selenophenyl ribofuranoside (10) via the tetraester (9) in 71 % isolated yield for the four steps. Treatment of (10) with tributylstannane and AIBN furnishes in 84 % yield the tribenzoyl 2–deoxy–L–ribofuranoside (11) which, on basic hydrolysis, gives 2–deoxy L–ribose (12) in high yield. In a third aspect of the invention, L–arabinose (13) is converted into 2–deoxy L–ribose (12) via the arabinopyranosyl bromide (14), via similar reductive rearrangement with tributylstannane to give the 2–deoxy ribopyranose tribenzoate (16). Hydrolysis yields 2–deoxy L–ribose. In a third aspect of the invention, L–arabinose is converted into 2–deoxy L–ribose by an alternate route.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 98/04302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	M.E.JUNG ET AL.: "Efficient Synthesis of L-Ribose and 2-Deoxy-L-Ribose from D-Ribose and L-Arabinose." TETRAHEDRON LETTERS., vol. 38, no. 24, 1997, OXFORD GB, pages 4199-4202, XP004074789 see the whole document ---	1-21
A	CHEMICAL ABSTRACTS, vol. 119, no. 25, 20 December 1993 Columbus, Ohio, US; abstract no. 271608c, J.KUBALA ET AL.: "Method of Preparing Optically Active 2-Deoxy-L-Ribose." page 1049; column 1; XP002066659 see abstract & CS 274 394 A ---	1

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 June 1998	07. 09. 98

Name and mailing address of the ISA	Authorized officer
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1

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 98/04302

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 108, no. 19, 9 May 1988 Columbus, Ohio, US; abstract no. 167793w, R.A.GAKHOKIDZE ET AL.: "Synthesis of 2-Deoxyribose." page 684; column 2; XP002066660 see abstract & ZH. ORG. KHIM., vol. 23, no. 5, 1987, pages 1126-1127, ---	1
A	CHEMICAL ABSTRACTS, vol. 122, no. 5, 30 January 1995 Columbus, Ohio, US; abstract no. 56398r, J.KUBALA ET AL.: "Process for Preparing L-Ribose." page 1231; column 2; XP002066661 see abstract & CS 275 890 A -----	1

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INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/US 98/04302

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
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2. ☐ Claims Nos.:
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3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-21

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-21

   Method for converting D-ribose into L-ribose or 2-deoxy-L-ribose.

2. Claims: 22-26

   Method for converting L-arabinose into 2-deoxy-L-ribose.

3. Claims: 27-33

   Method for converting L-arabinose into 2-deoxy-L-arabinose.